PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 501705/PXM/law	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416).
International Application No. **PCT/AU2003/001164**	International Filing Date *(day/month/year)* 5 September 2003	Priority Date *(day/month/year)* 5 September 2002
International Patent Classification (IPC) or national classification and IPC **Int. Cl.**[7] C12N 15/12, 15/52, 9/00, C07K 14/47, 16/18, 16/42, G01N 33/48, 33/50, 33/68		
Applicant GARVAN INSTITUTE OF MEDICAL RESEARCH et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   [X] This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 1 sheet(s).

3. This report contains indications relating to the following items:

   - I [X] Basis of the report
   - II [ ] Priority
   - III [X] Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV [X] Lack of unity of invention
   - V [X] Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI [ ] Certain documents cited
   - VII [ ] Certain defects in the international application
   - VIII [X] Certain observations on the international application

Date of submission of the demand 1 April 2004	Date of completion of the report 22 December 2004
Name and mailing address of the IPEA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. (02) 6285 3929	Authorized Officer **Philippa Wyrdeman** Telephone No. (02) 6283 2554

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International application No.
PCT/AU2003/001164

I. Basis of the report

1. With regard to the **elements** of the international application:*

☐ the international application as originally filed.

☒ the description, pages **1-150,** as originally filed,
pages , filed with the demand,
pages , received on with the letter of

☒ the claims, pages **151-166,** as originally filed,
pages , as amended (together with any statement) under Article 19,
pages , filed with the demand,
pages **167,** received on **30 June 2004** with the letter of **30 June 2004**

☐ the drawings, pages **1/64-64/64,** as originally filed,
pages , filed with the demand,
pages , received on with the letter of

☐ the sequence listing part of the description:
pages **1-95,** as originally filed
pages , filed with the demand
pages , received on with the letter of

2. With regard to the **language,** all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages

☐ the claims, Nos.

☐ the drawings, sheets/fig.

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

** *Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report*

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III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be nonobvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos: **63-74**

because:

☒ the said international application, or the said claims Nos. **63-74** relate to the following subject matter which does not require an international preliminary examination *(specify)*:

Claims 63-74, relate to agents that modulate EDD, the claims were only searched as they relate to the use of derivatives of EDD, eg ribozymes, siRNA, antibodies etc that are based on the EDD sequence. This is because the claims that include the use of other unspecified agents that are not necessarily derived from the EDD, are not limited to the technical features of the invention.

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for said claim Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

   ☐ restricted the claims.

   ☒ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☒ not complied with for the following reasons:

   The claims define 24 inventions.

   (See attached page)

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

   ☒ all parts.

   ☐ the parts relating to claims Nos.

Supplemental Box IV
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of Lack of Unity:

The inventions fall into two broad categories:

Category 1
Claims 1-26 and 63-75 broadly define methods of detecting cancer by assessing the expression of nucleic acids at locus 8q22.3. Narrower dependent claims define detection of EDD and/or p53R2 at 8q22.3

Methods of cancer detection at 8q22.3, therefore there are two inventions:
i. Detection of cancer comprising assessing levels of EDD.
ii. Detection of cancer comprising assessing levels of p53R2.

Category 2
Claims 27-62 define peptide complexes comprising EDD and cell cycle modulatory (eg topIIb), tumour suppressor (eg progesterone receptor), nuclear targeting (eg importin alpha 5) or DNA damage or repair peptides (eg calcium and integrin binding protein).

Although the claims share a feature of peptide complexes comprising EDD, this feature is known, see Henderson *et al.* Furthermore, even if claims were to be divided into inventions relating to complexes comprising EDD and cell cycle modulatory (1), nuclear targeting (2), DNA damage or repair (3), tumour suppressor (4), these features are also known, see Henderson *et al* or Honda *et al.*
Therefore, there are at least 22 different inventions consisting of complexes of EDD and:
CDS1, p53(TP53), TNF-alpha, HSP70, estrogen receptor, androgen receptor, progesterone receptor (SEQ ID NO 15), HRAS1-VNTR, CHK2 (SEQ ID NO 19), BRCA1, BRCA2 (SEQ ID NO 23), AIB1, NAT1, NAT2, XRCC1, XRCC2, XRCC5, CIB (SEQ ID NO 17), importin alpha 1 (SEQ ID NO 9), importin alpha 2 (SEQ ID NO 11), importin alpha 3 (SEQ ID NO 13), cdc25, cdc2a, cyclin-dependent kinase (cdk), cdk-inhibitor, mitogenic cyclins (A, B, C, D etc), MLH1, MSH2, and ATM.

In total, there are at least 22 inventions in category 2. Although some of the alternatives listed can be grouped together ie importins alpha 1, 2 and 3, independent members of some of these groups are known as complexes with EDD, thereby leading to lack of unity within the group.

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V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	**6-11, 13-26, 29-31, 35, 36, 40-50, 55-62 and 75**	**YES**
	Claims	**1-5, 12, 27, 28, 32-34, 37-39 and 51-54**	**NO**
Inventive step (IS)	Claims	**19-26, 29-31, 35, 36, 40-42, 55-62 and 75**	**YES**
	Claims	**1-18, 27, 28, 32-34, 37-39 and 43-54**	**NO**
Industrial applicability (IA)	Claims	**1-75**	**YES**
	Claims		**NO**

2. Citations and explanations (Rule 70.7)

The invention lies in a method of detecting cancer by assessing levels of EDD and p53R2 nucleic acids linked to map position 8q22.3. An elevated level of the nucleic acid is indicative of cancer in the subject. The invention also includes protein complexes comprising the EDD protein and another protein selected from the group consisting of proteins having:

i) tumour suppressor activity

ii) cell cycle modulatory activity,

iii) associated with DNA repair or damage

iv) nuclear targeting ability and

v) that is a progesterone receptor

Citations:

The following documents identified in the International Search Report have been considered for the purposes of this report:

D1: Henderson, M. J., *et al*, The Journal of Biological Chemistry, (2002), 277 (29): 26468-26478.

D2: Honda, Y., *et al*, Journal of Biological Chemistry, (2002 Feb 1) 277 (5): 3599-605.

D3: Callaghan, M.J., *et al*, Oncogene (1998 Dec 31) 17 (26): 3479-91.

D4: Richter, J., *et al*, Cancer Research, (1999 Nov 15) 59 (22): 5687-91.

D5: Tosi, S., *et al*, Genes, Chromosomes and Cancer, (1999 Mar) 24 (3): 213-21.

D6: Forozan, F., *et al*, British Journal of Cancer, (1999 Dec) 81 (8): 1328-34.

D7: Larramendy, M. L., *et al*, Cancer Genetics and Cytogenetics, (2000 Jun) 119 (2): 132-8.

D8: Clancy, J. L., *et al*, Oncogene, (2003 Aug 7) 22 (32): 5070-81.

Novelty:

Claims 1-5, 12, 27, 28, 32, 34, 37-39 and 51-54, are not novel in light of the prior art documents D1 to D3 and D5.

D5 teaches of detection of abnormalities in the 8q22.3 region of the human chromosome (abstract; table 1; page 220, col 1, para 3). Using the FISH method the citation shows amplification of nucleic acids in the 8q22.3 qter in cancer cells, as such the citation discloses all the essential features of claims 1-5 and 12.

Supplemental Box V
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of 2 (Novelty)

D1 teaches of protein complexes (abstract, introduction) comprising EDD-importin alpha 5 (page 26470, col 2, para 3), EDD-progesterone receptor (PR) (page 26473, col 2, para 2) and EDD-CIB/KIP (page 26474, col 2). The citation also teaches of methods of isolating the protein complexes using GST fusion proteins (page 26470 -materials and methods) as such, the citation anticipates claims 27, 28, 32, 34, and 51-54

D2 discloses the interaction between hHYD (EDD) and TopBP1 containing the C-terminal domain of BRCA1which is involved in DNA damage responses and check point mediated responses (introduction; page 3599, col 2, para 2). The materials and methods section also teaches of antibodies to hHYD (EDD) and to TopBP1 and therefore claims 27, 37-39, and 51-54 are not novel in light of this citation. D3 also teaches of an antibody to EDD, which would inherently have the property of binding to EDD-protein complexes, therefore, claims 37-39 are not novel.

D8 discloses all the essential features of claims 1-26, the citation discloses the identification and sequence of EDD located at chromosome 8q22.3 and that EDD mRNA and protein are frequently over expressed in breast and ovarian cancer. The citation was published after the priority date and therefore cannot be used as a novelty or inventive step citation. However, should the validity of the present application's priority come into question, the citation may become relevant.

Inventive Step:

The invention defined in claims 1-18 and 43-50 does not involve an inventive step in the light of D3-D7.
Claims 1-74 relate to a method of detecting cancer in a cell by determining the level of nucleic acid linked to map position 8q22.3.

Citation D3 teaches of the expression of increased EDD mRNA in breast cancer cell lines, the sequence of EDD given in the citation is the same as that disclosed in SEQ ID NO: 2 of the invention. Although the citation does not provide a method for detecting cancer cells it provides a sign post to determining the level of nucleic acid linked to the map position 8q22. The citation also teaches of amplification of the 8q22 region in cancers by hybridisation techniques using primers. It is routine practice to use primers that hybridise to a certain nucleic acid sequence in hybridisation studies. Although the citation does not disclose the specific primers listed in the claims, there is nothing in the specification to suggest that the primers provide unexpected advantages that are not produced by the cited primers or their technical equivalents. Therefore the PSA would directly and without difficulty, by routine steps, have produced the invention claimed in claims 1-18.

Similarly D4, D5, D6 and D7 disclose over representation of the 8q region in a number of cancer cells eg bladder cancer in D4 (introduction; page 5687), D6 teaches of localised DNA amplification in breast cancer cells at the region 8q22-q24.1 which includes the 8q22.3 region. It also teaches of using CCH and FISH techniques to determine the amplification (abstract; page 131, col 2, lines 5-7; page 1332, col 1, lines 7-12; page 1333, col 1, lines 9-21). D7 also discloses techniques similar to D6 and the amplification at 8q22 qter (abstract; Table 1; page 135, col 1, lines 9-11; page 136, col 1, para1, col 2; discussion). As such claims 1-5 are not inventive in light of citations D4, D6 and D7.

Claims 43-50 relate to a kit for detecting or producing a protein complex. The use of the term "for" in the claims does not restrict the claims to a specific use, it simply defines a kit comprising independent integers capable of use in detecting or producing protein complexes, therefore there is no limitation on the use of the kit. Further the integers that make up the kit i) the EDD polypeptide or a portion of the EDD polypeptide, ii) polypeptides selected from group consisting of proteins having tumour suppressor activity, cell cycle modulatory activity, associated with DNA repair or damage, nuclear targeting ability and that is a progesterone receptor, and iii) antibodies to these proteins or EDD are all well known in the art.
Therefore there does not seem to be an inventive step involved in putting two known integers together in a kit. Whilst there may be patentable subject matter when known integers are applied simultaneously or sequentially to produce a new product or interacting mixture, the claims have not defined how the kit or pack, by its construction, will in normal use ensure the simultaneous or sequential application of the integers.

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

Claims 37, 42 and 44 are not fully supported by the specification. The claims relate to antibodies that bind to protein complexes comprising the EDD protein. The invention appears to be complexes of EDD with polypeptides selected from group consisting of proteins having tumour suppressor activity, cell cycle modulatory activity, associated with DNA repair or damage, nuclear targeting ability and that is a progesterone receptor. The claims, however, include all protein complexes of EDD weather they contain the specific polypeptides mention above or not, as such, this includes any protein that would bind with EDD even if it does not belong to the class of polypeptides that makes up the invention.

Claim 69 - 74 are not fully supported by the specification. The claims relates to an antisense nucleic acid, ribozyme, PNA, interfering RNA or siRNA that is 80% homologous to SEQ ID NO: 47. The invention is either a method of detecting cancer by quantitating the amount of EDD nucleic acid present in the cell or protein complexes of EDD. SEQ ID NO: 47 relates to a synthetic siRNA that does not seem to have any relation to detecting EDD nucleic acid concentration in the cell or to a method of reducing the expression of EDD in a cancer cell.

Claim 52 is not clear. The claim relates to a method of isolating a protein complex comprising an EDD protein and a protein selected from the group of proteins having tumour suppressor activity, cell cycle modulatory activity, associated with DNA repair or damage, nuclear targeting ability and that is a progesterone receptor. It appears from the claim that the complex must contain the EDD protein. However, steps i) to iii) disclose two different proteins and none of them is EDD.

Claim 75 is not fully supported by the specification. The claim relates to a method of determining the ability of a cell to phosphorylate CHK2 in response to a DNA damaging agent by determining the level of expression of EDD in the cell. The invention lies in a method of detecting cancer by quantitating the amount of EDD nucleic acid present in the cell or protein complexes of EDD. As such, the claim appears to lack the special technical feature of the invention- a method of detecting cancer by quantitating the amount of EDD expression or the different protein complexes of EDD.

Claims 53 and 54 are not clear. It is not clear which protein is being referred to in the claims.

complementary, in whole or in part, to EDD-encoding RNA.

68. The method of claim 67 wherein the antisense nucleic acid, ribozyme, PNA, interfering RNA or siRNA comprises a sequence that is complementary to at least about 15-20 contiguous nucleotides of a sequence having at least 80% identity to SEQ ID NO: 1 or SEQ ID NO: 3.

69. An antisense nucleic acid, ribozyme, PNA, interfering RNA or siRNA comprising a sequence having at least 80% homology to SEQ ID NO: 47.

70. The use of the antisense nucleic acid, ribozyme, PNA, interfering RNA or siRNA of claim 69 to reduce the expression of EDD in a cell.

71. The use of the antisense nucleic acid, ribozyme, PNA, interfering RNA or siRNA of claim 69 to inhibit cellular proliferation.

72. A pharmaceutical composition comprising the antisense nucleic acid, ribozyme, PNA, interfering RNA or siRNA of claim 69.

73. The use of the composition of claim 72 to reduce the expression of EDD in a cell.

74. The use of the composition of claim 72 to inhibit cellular proliferation.